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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/410,462	10/01/1999	ANGELICA WILLIAMS	ONYX1046-ORD	6889

37499 7590 07/25/2005

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EXAMINER	
ANGELL, JON E	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 07/25/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	Application No. 09/410,462	Applicant(s) WILLIAMS ET AL.	
	Examiner Jon Eric Angell	Art Unit 1635	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 20 June 2005 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☐ The period for reply expires _____months from the mailing date of the final rejection.
   b) ☒ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☒ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☒ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: *See Continuation Sheet*. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☒ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1-20,22-24 and 26-28*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). _____
13. ☐ Other: _____.

Anne-Marie Falk
Jon Eric Angell
ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER

Continuation of 3. NOTE: Claims 22-24 and 26-28 are rejected under 35 USC 112, 2nd paragraph because the instant claims depend on cancelled claims, thus rendering the instant claims indefinite. The proposed amendment to claims 22-24 and 26-28 filed 6/20/2005 is acknowledged. It is noted that the proposed amendment would overcome the 112, 2nd paragraph rejection. However, the proposed amendment will not be entered because the amendment would add limitations that are not currently present in claims 22-24 and 26-28. Since the new limitations are not currently present in the pending claims, additional search and/or consideration would be required with respect to the new limitations .

Continuation of 11. does NOT place the application in condition for allowance because: With respect ot the rejection of claims under 35 USC 112, 1st paragraph, Applicants request clarification of the rejection as Applicants believe that the rejection has become a "moving target". In order to clarify the "moving target" of the rejection, it is respectfully pointed out that the rejection has only changed in scope from a complete lack of enablement for in vivo embodiments other than direct intratumoral injection into a tumor in a nu/nu nude mouse (as set forth in the Office Action mailed 9/15/00) to a lack of enablement for in vivo embodiments by any route of administration other than direct intratumoral delivery (as set forth in the Office Action mailed 1/17/02). It is respectfully pointed out that the Office Action dated 9/15/00 clearly set forth that the the claims are enabled for "a replication competent adenovirus comprising a mutation in the E1A-CR2 region, wherein said adenovirus is dl922/947, or dl1107 or pm928..." (Emphasis added; see page 2, at lines 3-4 of paragraph number 3). Furthermore, the Office Action dated 9/15/00 also indicates reasons why the claims are only enabled for the specific indicated adenoviruses (e.g., see last paragraph of page 5). Specifically, the Examiner indicated that, "The specification lacks guidance to the breadth of the claims regarding the mutant adenovirus of the instant, and its ultimate functioning in an in vivo method of (a) substantially and selectively killing dividing cells... The specification gives guidance for the construction of said mutants, but the claims encompass any in vivo adminstration of said mutant, which may not necessarily reflect similar functioning..." Thus, the Examiner has indicated that the claims are broad with respect to the mutant adeoviruses encompassed by the claims and that the specification, although it has provided guidance for making the mutant adenoviruses, the mutant viruses may not have the same function. Since it was indicated that the claims are enabled for dl922/947, dl1107, or pm928 (e.g., see page 2 at paragraph 3) and in view of the rejection as a whole, the only mutants that the examiner has clearly indicated are enabled are dl922/947, dl1107 and pm928. The Examiner indicated the reasons why the claims are not enabled for the in vivo embodiments in the Office Action dated 9/15/2000 (see pages 2-9 of the 9/15/2000 office Action) and further clarified the rejection in the Office Action dated 6/5/2001 by stating, "The point that applicants are required to teach via in vivo examples is that in a cell population comprising dividing and quiescent cells, a method for substantially and selectively killing dividing cells without the concomitant killing of non-dividing cells." (See page 3 of the 6/5/2001 Office Action). As such, the Examiner indicated that the claimed methods were not enabled for the in vivo embodiments because because there was no indication that the broadly claimed method would predictably result in substantially and selectively killing dividing cells without the concomitant killing of non-dividing cells. Upon further consideration, however, the Examiner determined that direct intratumoral injection of the indicated mutant adenoviral vectors would sufficiently limit the claimed method such that it would result in substantially and selectively killing dividing cells without the concomitant killing of non-dividing cells as indicated in the Office Action dated 1/17/2002 (see pages 2-3). Therefore, the reasons set forth in the Office Actions dated 9/15/2000, 6/5/2001 and 1/17/2002 indicate the reasons why the instant claims are enabled for a method of reducing the size of a tumor by intratumoral injection of the Ad5 vector disclosed as dl922/947, dl1107 or pm928, but not for the full scope encompassed by the claims.

With respect to Applicants arguments that identification and characterization of adenoviral mutants useful in the practice of the present invention are extensively discussed in the specification, it is noted that the indicated passages of the specification which the Applicants refer to have been reviewed and do not appear to disclose any specific mutant adenoviral vectors other than the dl922/947, dl1107 and pm928 mutants. As such, it idoes not appear that the specification has identified and characterized any specific mutants other than dl922/947, dl1107 and pm928.

With respect to the Applicants arguments regarding the Examiner's assesment of Example 4, it is acknowledged that the standard for enablement is not that all possible species are exemplified and operable. However, as indicated by the Examiner in the Office Action dated 6/5/2001 (see page 3) Example 4 discloses intranasal inoculations of the mutant or wild type adenovirus and indicates that the intranasally administered mutant adenovirus divides less in the quiescent lung cells than the wild type virus. Example 4 does not demonstrate that the intranasal administrtation of the mutant adenorial vector results in substantially and selectively killing dividing cells without the concomitant killing of non-dividing cells. Furthermore, it was pointed out in the Office Action dated 4/20/2005 that the claims encompass treating any tumor by any route of administration. As such, in order for Example 4 to be enabling for the full scope encompassed by the claims it would have to demonstrate that intranasal delivery could be used to specifically and effectively deliver the mutant adenoviral vectors to the target tumor cells wherein the target tumor cells can be any type of tumor such as a brain tumor such that the method results in substantially and selectively killing dividing cells without the concomitant killing of non-dividing cells. Therefore, the Examiner is not relying on improper standards for enablement. The enablement determination was not based solely on the breadth of the claims, but on a combination of factors including the nature of the invention, the state of the prior art, the amount of direction or guidance presented, the quantity of experimentation necessary, as well as the breadth of the claims.

With respect to Applicants arguments that the claims are not rejected for the reasons of record, it is respectfully pointed out that Applicants have only indicated the consideration of the Office Action dated 6/5/2001 and have not indicated consideration of the Office Actions dated 9/15/2000 and 1/17/2002. The Office Action dated 1/17/2002 clearly indicates, "Claims 1-24 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of substantially and selectively reducing tumor size by the intratumoral injection of Ad5 adenoviral vectors d1922/947 or dl1107 or pm928, does not reasonably provide enablement for other limitations encompassed by the claims." The instant rejection is consistent with the rejection as indicated in the 1/17/2002 Office Action, and relies on the reasons of record set forth and modified throughout prosecution including reasons set forth in the 9/15/200, 6/5/2001 and 1/17/2002 Office Actions, as indicated above.

With respect to Applicants arguments regarding U.S. Patent No. 5,677,178, the Examiner would like to clarify the statement made in the 6/20/2005 Office Action. First, the Examiner incorrectly stated that the '178 patent was not enabled for any route of administration other than direct delivery to the tumor cells. The Examiner should have stated that the '178 patent is not sufficient to overcome the enablement rejection of the instant case. In no way did the Examiner mean to indicate that the '178 is not fully enabled. Therefore, the Examiner withdraws the comments directed to the scope of enablement of the U.S. Patent No. 5,677,178. The '178 patent, however, is not sufficient to overcome the enablement rejection of the instant case as it does not overcome the rejection as it pertains to the breadth of the mutant adenoviral vectors encompassed by the claims and using the mutant adenoviral vectors encompassed by the claims to substantially and selectively kill the dividing cells without the concomitant killing of non-dividing cells when the viral vectors are administered by any route of administration other than direct intratumoral delivery. It is noted that each application is examined on its own merits.

With respect to the rejection of claims under 35 USC 102(e), Aplicants argue that Bischoff et al. does not teach substantial and slective killing of dividing cancer and endothelial cells. As indicated in the Office Action dated 6/20/05, Bishoff teaches treating cancer by administering a mutant adenovirus encompassed by the claims to a tumor in an animal (e.g., see column 10, lines 10-42; column 16, lines 18-67; column 17, lines 1-35; column 18, line 30 through column 19, line 56, etc.). Applicant is reminded that MPEP 2112.02 indicates, "When the prior art device is the same as a device described in the specification for carrying out the claimed method, it can be assumed the device will inherently perform the claimed process. In re King, 801 F.2d 1324, 231 USPQ 136 (Fed. Cir. 1986)." In the instant case, Bishoff teaches a method comprising administering a vector encompassed by the claims to a tumor in an animal. It is noted that tumors comprise dividing cancer cells and dividing endothelial cells (e.g., vascular cells of the tumor). Therefore, the method taught by Bishoff must, by necessity, result in killing of the dividing cells of the tumor, which would include dividing cancer cells and dividing endothelial cells. Therefore, Applicants arguments are not persuasive and the rejection is not withdrawn. .